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Pharmacological Characterization of Psychosis-Like Behavior in the MPTP-Lesioned Nonhuman Primate Model of Parkinson's Disease

Naomi P. Visanji, PhD,[1] Jordi Gomez-Ramirez, PhD,[1] Tom H. Johnston, PhD,[1] Donna Pires,[1] Valerie Voon, MD,[2] Jonathan M. Brotchie, PhD,[1] and Susan H. Fox, MD, PhD[3]*

[1]*Toronto Western Research Institute, Toronto Western Hospital, Toronto, Canada*
[2]*Department of Psychiatry, Toronto Western Hospital, Toronto, Canada*
[3]*Division of Neurology, University of Toronto, Toronto, Canada*

Video 

Abstract: Investigation of the pathophysiology of psychosis in Parkinson's disease (PD), as well as the assessment of potential novel therapeutics, has been limited by the lack of a well-validated animal model. MPTP-lesioned primates exhibit abnormal behaviors that are distinct from dyskinesia and parkinsonism and may represent behavioral correlates of neural processes related to psychosis in PD. Here we assess four types of behavior—agitation, hallucinatory-like responses to nonapparent stimuli, obsessive grooming, and stereotypies that are termed "psychosis-like"—and define their pharmacology using a psychosis-like behavior rating scale. By assessing the actions of drugs known to enhance or attenuate psychosis in PD patients, we find that the pharmacology of these behaviors recapitulates, in several respects, the pharmacology of psychosis in PD. Thus, levodopa and apomorphine elicited psychosis-like behaviors. Amantadine significantly decreased levodopa-induced dyskinesia but exacerbated psychosis-like behaviors. Haloperidol reduced psychosis-like behaviors but at the expense of increased parkinsonian disability while the atypical neuroleptics clozapine and quetiapine reduced psychosis-like behaviors without significant effect on parkinsonian disability. The response of different components of the psychotomimetic behavior suggested the involvement of both dopaminergic and nondopaminergic mechanisms in their expression. © 2006 Movement Disorder Society

Key words: Parkinson's disease; psychosis; animal model; MPTP-lesioned primate

Current medical and surgical treatments for Parkinson's disease (PD) are generally effective at providing sustained reversal of motor symptoms. However, nonmotor symptoms remain a major challenge in treating patients with advanced PD.[1] Of these, neuropsychiatric problems are now the leading cause of morbidity in PD[2] and can affect up to 30% to 40% of patients.[3] In particular, psychosis in PD is often cited as the main reason for admission to nursing home care.[4,5]

The pathophysiology underlying psychosis in PD is unknown; however, the main risk factors for developing psychotic symptoms include disease duration and severity, age, and cognitive impairment.[6,7] Symptoms of psychosis include a range of illusions, minor hallucinations, and well-formed hallucinations (particularly visual hallucinations) and delusions. All antiparkinsonian medications, particularly dopamine receptor agonists, can induce hallucinations in susceptible PD

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*Correspondence to: Dr. Susan H. Fox, Division of Neurology, Movement Disorders Clinic MCL7-421, Toronto Western Hospital, 399, Bathurst Street, Toronto, Ontario M5V 2S8, Canada.
E-mail: sfox@uhnresearch.ca

Current address for Dr. Voon: Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA.

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patients.[3] The psychotic symptoms may resolve on reducing or discontinuing the offending drug suggestive of an underlying dopaminergic mechanism. However, the etiology is likely multifactorial and a dopaminergic drug-induced phenomenon is likely insufficient as an explanation. For instance, early drug-induced hallucinations are often associated with subsequent cognitive and psychiatric problems.[8] In addition, rather than a strict association with blood levels of dopamine, visual hallucinations will fluctuate through the day and are most commonly reported in the evening and overnight,[6,9] and in questionnaire studies of prevalence of nonmotor fluctuations, some patients experience hallucinations specifically related to *off* periods.[10,11] Thus, psychosis may to be due to an as yet poorly defined underlying disease process rather than purely a dopaminergic drug-induced phenomenon. One such process may involve changes in 5-HT receptors. Thus, postmortem tissue studies have shown a relative preservation of 5-HT_2 receptors in the temporal cortex in patients with cortical Lewy body dementia and hallucinations compared to patients without hallucinations.[12] This is of interest as this brain region has been implicated in psychosis in PD, Lewy bodies being increased in the amygdala and parahippocampus of the temporal lobe in PD patients with hallucinations compared to those without.[13]

Treatment of psychosis in PD has traditionally focused on dopamine D_2 receptor blockade, a rationale based on the understanding from other psychiatric conditions such as schizophrenia, rather than psychosis in PD itself. However, dopamine D_2 receptor antagonism using "typical" neuroleptics (e.g., haloperidol) will exacerbate parkinsonism.[14] Thus, recent treatments have aimed at using "atypical" neuroleptics, which are thought to have a reduced tendency to exacerbate parkinsonism. However, some atypical neuroleptics, such as olanzapine and risperidone, are less effective than haloperidol at reducing psychotic symptoms and have also been shown to exacerbate parkinsonism.[15–17] Clozapine, to date, is the most effective treatment in reducing psychosis in PD without exacerbating parkinsonism,[18,19] but with the safety issue of potential blood dyscrasias.[20] Quetiapine has been widely used for psychosis in PD due to lack of such side effects and little tendency for exacerbation of parkinsonian symptoms, though clinical studies have shown it to be both effective and ineffective.[21] Thus, the treatment of psychosis in PD remains problematic.

A major obstacle to investigating the neural mechanisms underlying psychosis in PD and also assessing potential therapeutic options is the lack of a validated animal model of psychotic behavior in PD. Animal models of psychotic symptoms in conditions such as schizophrenia are not necessarily translatable to PD as there is no indication that the underlying neuropathology and physiology are the same and most models are induced by a specific and acute pharmacological challenge.[22,23] The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–lesioned primate is a well-characterized model of the motor symptoms of PD that has been extensively used to investigate the neural mechanisms underlying parkinsonism and dyskinesia.[24] We have also observed that the MPTP-lesioned primate, following long-term treatment with levodopa, will often experience abnormal psychotomimetic behaviors that are in addition to and distinct from dyskinesia. We propose that these behaviors may represent a model of psychosis-like behavior in PD.[25] The phenomenology of these behaviors is similar to that observed in chronic low-dose amphetamine-treated primates, an animal model of schizophrenia, where stereotypies, hypervigilance, tracking nonapparent stimuli, constant checking, and grasping movements are reported.[26,27] We have characterized the abnormal psychotomimetic behaviors seen in the MPTP-lesioned primate into four categories—agitation, hallucinatory-like behaviors, obsessive activity, and stereotypies—and have devised a psychosis-like behavior rating scale (Table 1).

The present study was undertaken to validate this proposed model of psychosis-like behavior in PD, using drugs that are known either to increase or to decrease psychosis in PD patients and distinguish this behavioral response from the well-established ratings of dyskinesia and parkinsonian disability.

MATERIALS AND METHODS

The protocol employed to produce a marmoset model of advanced parkinsonism was as described previously.[28,29] This advanced level of lesion was chosen as it is at such a stage that PD patients are more prone to develop psychotic symptoms. Briefly, seven female marmosets (*Callithrix jacchus*; 350–425 g) obtained from Harlan (Indianapolis, IN) were treated with MPTP (2 mg/kg s.c. for 5 consecutive days). Animals were housed in groups and cared for under an approved local institution protocol (UHN 02/053) in accordance with the regulations defined by the Canadian Council on Animal Care. The animals were kept in controlled housing conditions, with constant temperature (25°C), relative humidity (50%), and 12-hour light/dark cycles (08:00–20:00 lights on). The animals had free access to food, fresh fruit supplements, and water. Following stabilization of the parkinsonian state (12 weeks), characterized by bradykinesia, hunched posture, reduced attention, and a reduced range of movement, animals were treated with

TABLE 1. *MPTP-lesioned marmoset psychosis-like behavior rating scale*

Category of behavior	Description	Score (rated each min) Absent	Present
1. Agitation	a. Hyperkinesia: fast, driven, relentless running movements, variable direction.	0	1
	b. Vocalization (> 10 s/min)	0	1
2. Hallucinatory-like response to apparent nonstimuli	a. Tracking: following non-apparent stimuli (> 10 s/min)	0	1
	b. Staring: head still, looking in one direction for extended period (> 10 s/min)	0	1
3. Obsessive grooming	a. Scratching or grooming repetitively (> 2 times/min)	0	1
4. Stereotypies	a. Side-to-side jumping: quick jumping movements repeated (> 2 times/min)	0	1
	b. Head checking movements: quick, darting side-to-side, exaggerated large-amplitude head movements, repeated, with body movements (> 3 times/min)	0	1
	c. Purposeless running, jumping in circles (> 2 times/min)	0	1
	d. Fiddles with bars: repetitive grasping at bars (> 2 times/min)	0	1

levodopa as Prolopa (15 mg/kg levodopa and 3.75 mg/kg benserazide p.o.) twice daily for 3 weeks. This study was part of other ongoing studies involving long-term treatment with levodopa to minimize animal usage and was performed 8 months after the start of MPTP treatment. Animals had stable parkinsonism for at least 6 months before commencement of this study. A 30-day washout period after previous drug studies was allowed prior to the commencement of the present study.

On each experimental day, at 9 AM, animals received levodopa methyl ester (15 mg/kg with 3.75 mg/kg benserazide s.c.) in conjunction with a test compound or vehicle and were then placed singly in observation cages (0.8 m × 0.8 m × 0.7 m) with a single branch, a small dish of fruit, and a water bottle. The animals' behavior was then recorded for a period of 2 hours, using a digital video camera connected to a DVD recorder, for posthoc assessment by an observer blinded to the treatment condition. Ratings were performed in two 10-minute time periods representing the time of peak effect of levodopa (40–50 and 70–80 minutes after levodopa). Due to the shorter duration of action, the apomorphine peak effect was taken at 10–20 and 40–50 minutes after dose.

Parkinsonian disability was scored using the scale as previously described, consisting of range of movement (score 0–9), bradykinesia (0–3), posture (0–1), and attention (0–1).[28–30] The score assigned in each time period was the most prevalent activity and parkinsonian disability was calculated using the following formula: (range of movement × 1) + (bradykinesia × 3) + (posture × 1) + (attention × 9). The maximum score per 10-minute time frame = 36; a normal animal scores < 6. For graphical representation of total peak-dose scores, parkinsonian disability was expressed as absent (score 0); mild (score 1–18) where an animal would have normal range of movement, slight or no bradykinesia, no postural abnormalities, and normal alertness; and moderate (score 19–36) where bradykinesia would be present, some reduced range of movement, posture normal, and alertness normal. Marked (score 37–54) would indicate bradykinesia and postural abnormalities, reduced range of movement, and some reduced alertness; severe (score 55–72) would indicate akinetic, hunched posture, little or no movement, and absent alertness.

Dyskinesia was rated using a dyskinesia disability rating scale (score 0–4) as previously described.[28–30] Chorea and dystonia were rated separately and added to give a total dyskinesia score; maximum possible score per 10 minutes = 8. For graphical representation of total peak-dose scores, dyskinesia disability was expressed as absent (score 0); mild (score 1–4), nondisabling dyskinesia present < 30% time; moderate (score 5–8), nondisabling dyskinesia present > 30% time; marked (score 9–12), disabling dyskinesia present < 30% time; and severe (score 13–16), disabling dyskinesia present > 30% time.

Psychosis-like behaviors were rated during the same time periods using the MPTP-lesioned marmoset psychosis-like behavior rating scale (Table 1).[25,31] Nine different behaviors (in the four categories) were rated. Each activity was scored, 0 = absent or 1 = present, per minute for the same 10-minute time period in which parkinsonism and dyskinesia were rated and accumulated to give a total psychosis-like behavior score (maximum possible score for each individual behavior = 10; total possible maximum psychosis-like behavior score per 10 minutes = 90).

A dose response to levodopa methyl ester (10.0 and 15.0 mg/kg s.c. [+ benserazide 2.5 and 3.75 mg/kg, respectively]) was assessed. Amantadine (0.1–10 mg/kg s.c.),[32] clozapine (0.1–1.0 mg/kg s.c.),[33] and haloperidol (0.01–0.1 mg/kg s.c.)[34] were all administered with levodopa methyl ester 15 mg/kg (+ benserazide 3.75 mg/kg s.c.) at t = 0 minutes. Quetiapine (0.5–4.5 mg/kg p.o.)[35]

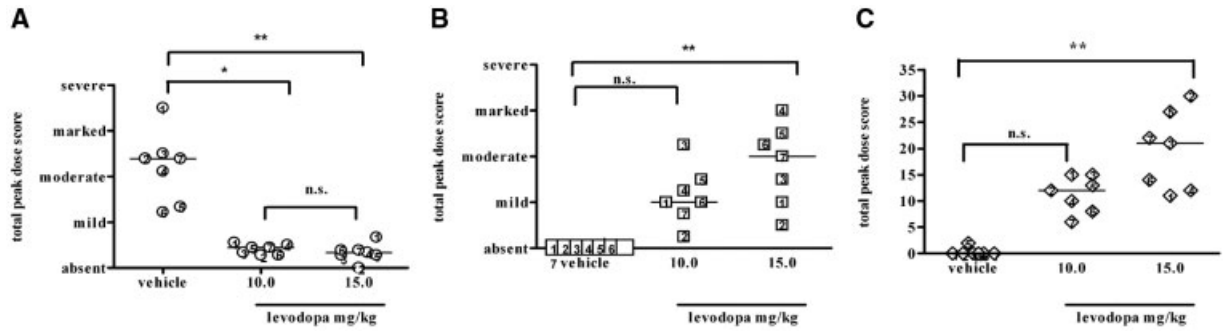

FIG. 1. Dose response effect of levodopa in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Peak-dose parkinsonian disability; **(B)** peak-dose dyskinesia; and **(C)** total peak-dose psychosis-like behaviors as measured using rating scales. Data show individual animals as denoted numerically within markers; bars represent median total peak-dose scores (40–80 min) following levodopa–methyl ester 10 and 15 mg/kg (+ benserazide) s.c. Asterisk, $P < 0.05$; double asterisk, $P < 0.01$, Friedman test followed by Dunn's multiple-comparison test; n = 7.

was administered 30 minutes prior to levodopa. Apomorphine (0.03 mg/kg s.c.) was administered alone.[34] All dosing volumes were 1 ml/kg. The order of drug administration was randomized using an incomplete Latin square design and testing was performed over 42 days with 2 to 5 days between dosing.

Statistical Analysis

Data from the two time points representing peak effect were cumulated and expressed as median total peak-dose score (±range). Data were analyzed using appropriate nonparametric one-way analysis of variance (Friedman or Kruskal–Wallis) and posthoc analysis using Dunn's multiple-comparison test. For the comparison of psychosis-like behaviors over time, a paired Wilcoxon signed-rank test was used. For assessing any correlation between the level of psychosis-like behavior and dyskinesia in each animal, in the levodopa dose response study, a nonparametric Spearman correlation was performed. For the apomorphine study, comparison to levodopa-induced psychosis-like behaviors and dyskinesia was made using an unpaired nonparametric Mann–Whitney test. Significance was set at $P < 0.05$ in all cases. Analyses were conducted with GraphPad Prism (version 4.0).

RESULTS

Following treatment with levodopa methyl ester (15 mg/kg + benserazide 3.75 mg/kg s.c.), all animals exhibited abnormal psychosis-like behavior that was distinct from dyskinesia and parkinsonism (see Video). Furthermore, normal non–MPTP-lesioned animals can exhibit head movements as part of normal alertness and may run around the cage and vocalize (see Video); however, the behaviors described and rated here as psychosis-like are repetitive, excessive, exaggerated, and driven. The abnormal repetitive nature of the movements is defined in the rating scale (Table 1).

Each animal exhibited a specific pattern of behavior in response to levodopa treatment that remained stable over several months. Thus, there was no difference between total peak-dose psychosis-like behavior scores following administration of levodopa methyl ester (15 mg/kg) at the end of the study compared to 6 months prior: median peak-dose score 12 (range, 7–31) and 16 (range, 9–30), respectively (Wilcoxon signed-rank test; n = 7; $P < 0.05$). The most common activity was stereotypic behavior. Each animal exhibited one or two such behaviors, usually repetitive exaggerated head checking associated with purposeless running in circles or around the cage and often with side-to-side jumping. Some animals exhibited repetitive scrabbling at the bars of the cage. All animals also exhibited staring and tracking behavior. Four of the animals exhibited agitation with hyperkinetic driven behavior consisting of jumping and running. Three animals exhibited excessive scratching.

Levodopa Dose–Response

There was a significant effect of treatment on peak-dose parkinsonian disability (Friedman test, $F_{(2,18)} = 11.14$; n = 7; $P < 0.001$). Levodopa methyl ester (10 and 15 mg/kg) significantly reversed peak-dose parkinsonian disability compared to vehicle (Dunn's multiple-comparison test, both P values < 0.05; Fig. 1A). There was no significant difference in peak-dose antiparkinsonian action between these two doses (Dunn's multiple-comparison test, $P > 0.05$; Fig. 1A). There was also a significant effect of treatment on peak-dose dyskinesia (Friedman test, $F_{(2,18)} = 12.07$; n = 7; $P < 0.0001$). However, only levodopa methyl ester 15 mg/kg significantly increased peak-dose dyskinesia compared to vehicle (Dunn's multiple-comparison test, $P < 0.01$; Fig. 1B).

In addition, there was a significant effect of treatment on peak-dose psychosis-like behaviors (Friedman test, $F_{(2,18)} = 12.29$; n = 7; $P < 0.001$). Only levodopa

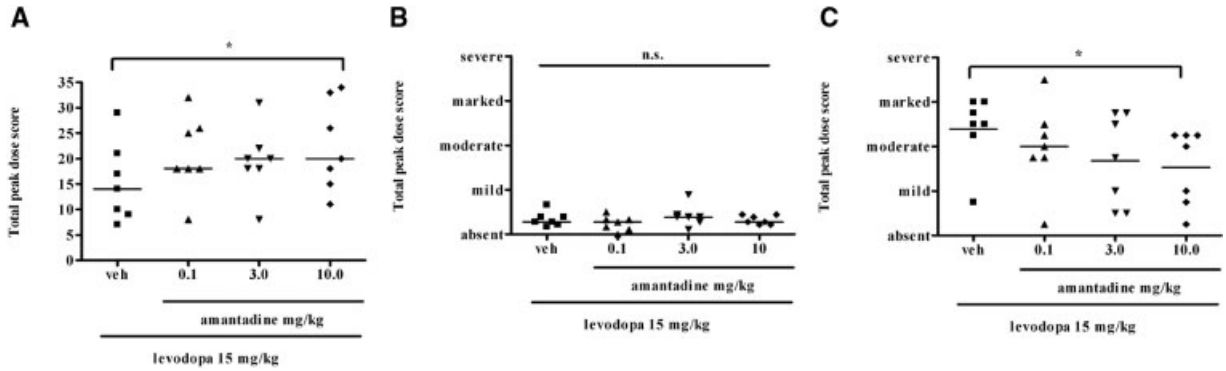

FIG. 2. Effect of amantadine and levodopa in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Total peak-dose psychosis-like behaviors; **(B)** peak-dose parkinsonian disability; and **(C)** peak-dose dyskinesia as measured using rating scales following administration of vehicle/amantadine 0.1, 3.0, and 10.0 mg/kg s.c. with levodopa methyl ester 15 mg/kg (+ 3.75 mg/kg benserazide) s.c. Data show individual animals; bars represent median total peak-dose scores at 40 to 80 minutes following drug administration. Asterisk, $P < 0.05$, Friedman test followed by Dunn's multiple-comparison test; n = 7.

methyl ester 15 mg/kg resulted in a significant increase in total peak-dose psychosis-like behavior scores compared to vehicle (Dunn's multiple-comparison test, $P < 0.01$; Fig. 1C). The increase in psychosis-like behavior with levodopa methyl ester 15 mg/kg compared to 10 mg/kg was due to a specific increase in stereotypies: median total peak-dose score 3 (range, 0–9) with levodopa methyl ester 10 mg/kg compared to 8 (range, 2–20) with levodopa methyl ester 15 mg/kg (Wilcoxon signed-rank test, n = 7; $P < 0.05$). One animal (Animal 5) treated with vehicle expressed a low level of tracking behavior; otherwise, no psychosis-like behaviors were seen following vehicle treatment.

Of note, there was no correlation between the severity of dyskinesia and psychosis in individual animals (Fig. 1B–C). Psychosis-like behaviors elicited by levodopa methyl ester at 10 mg/kg had no significant correlation with dyskinesia elicited by either levodopa methyl ester 10 or 15 mg/kg ($r^2 = 0.268$ and 0.143, respectively; both P values > 0.05). Similarly, psychosis-like behaviors elicited by levodopa methyl ester 15 mg/kg were not correlated with dyskinesia elicited by either levodopa methyl ester 10 or 15 mg/kg ($r^2 = 0.064$ and 0.046, respectively; both P values > 0.05). For example, Animal 2 had a mild dyskinesia but the highest peak-dose psychosis-like behavior.

Amantadine

Amantadine (0.1–10 mg/kg s.c.) coadministered with levodopa methyl ester 15 mg/kg significantly increased total peak-dose psychosis-like behavior (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,28)} = 8.250$; n = 7; $P < 0.05$; Fig. 2A). There was no effect on peak-dose antiparkinsonian efficacy with any dose of amantadine (Friedman test, $F_{(3,24)} = 6.955$; n = 7; $P > 0.05$; Fig. 2B). There was a significant effect of amantadine on peak-dose dyskinesia (Friedman test, $F_{(3,24)} = 10.20$; n = 7; $P < 0.05$; Fig. 2C). Amantadine 10 mg/kg significantly decreased total peak-dose dyskinesia compared to vehicle (Dunn's multiple-comparison test, $P < 0.05$).

Haloperidol

Haloperidol (0.01–0.1 mg/kg s.c.) coadministered with levodopa methyl ester (15 mg/kg s.c.) had a significant effect on total peak-dose psychosis-like behavior (Kruskal–Wallis followed by Dunn's multiple-comparison test, $F_{(3,22)} = 13.12$; n = 6 to 7; $P < 0.01$; Fig. 3A). Haloperidol 0.03 mg/kg and 0.1 mg/kg significantly reduced peak-dose psychosis-like behaviors compared to vehicle (Dunn's multiple-comparison test, $P < 0.05$ and < 0.01, respectively; Fig. 3A). This reduction in psychosis-like behaviors was due to a specific reduction in stereotypies with haloperidol 0.1 mg/kg compared to vehicle: median total peak-dose score 0 (0) and 6 (range, 1–25), respectively (Kruskal–Wallis followed by Dunn's multiple-comparison test, $F_{(3,22)} = 12.51$; n = 6 to 7; $P < 0.01$). However, haloperidol 0.1 mg/kg significantly increased peak-dose parkinsonian disability compared to vehicle (Kruskal–Wallis followed by Dunn's multiple-comparison test, $F_{(3,22)} = 9.937$; n = 6–7; $P < 0.05$; Fig. 3B) and resulted in a concomitant decrease in peak-dose dyskinesia (Kruskal–Wallis followed by Dunn's multiple-comparison test, $F_{(3,22)} = 14.15$; n = 6–7; $P < 0.01$; Fig. 3C).

Quetiapine

Quetiapine (0.5–4.5 mg/kg p.o.) coadministered with levodopa methyl ester (15 mg/kg s.c.) significantly reduced total peak-dose psychosis-like behavior (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,20)} = 9.915$; n = 6; $P < 0.05$; Fig. 4A). The most effective dose was 1.5

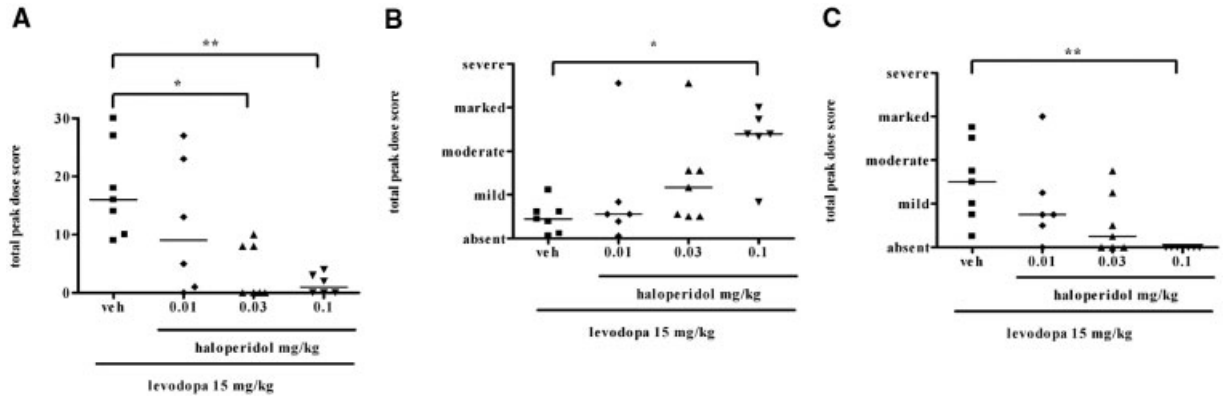

FIG. 3. Effect of haloperidol and levodopa in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Total peak-dose psychosis-like behaviors; **(B)** peak-dose parkinsonian disability; and **(C)** peak-dose dyskinesia as measured using rating scales following coadministration of vehicle/haloperidol 0.01, 0.03, and 0.1 mg/kg s.c. with levodopa methyl ester 15 mg/kg (+ 3.75 mg/kg benserazide) s.c. Data show individual animals; bars represent median total peak-dose scores at 40 to 80 minutes following drug administration. Asterisk, $P < 0.05$; double asterisk, $P < 0.01$, Kruskal–Wallis followed by Dunn's multiple-comparison test; n = 6–7.

mg/kg compared to 0.5 mg/kg (Dunn's multiple-comparison test, $P < 0.05$). Of note, the lowest dose of quetiapine, 0.5 mg/kg, reduced psychosis-like behaviors in three animals but in three animals there was an increase in psychosis-like behaviors. Quetiapine had no significant effect on peak-dose parkinsonian disability (Friedman test, $F_{(3,20)} = 1.024$; n = 6; $P > 0.05$; Fig. 4B). There was, however, a significant effect of quetiapine on peak-dose levodopa-induced dyskinesia (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,20)} = 7.661$; n = 6; $P < 0.05$; Fig. 4C).

Clozapine

Clozapine (0.1–1.0 mg/kg s.c.) coadministered with levodopa methyl ester (15 mg/kg s.c.) significantly reduced total peak-dose psychosis-like behavior (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,24)} = 10.71$; n = 7; $P < 0.05$; Fig. 5A). Both clozapine 0.3 mg/kg and 1.0 mg/kg significantly reduced peak-dose psychosis-like behaviors compared to vehicle (Dunn's multiple-comparison test, both P values < 0.05; Fig. 5A). The reduction in total psychosis-like behavior was due to a significant reduction in hallucinatory-like behavior (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,24)} = 8.063$; n = 7; $P < 0.05$). Clozapine had no significant effect on peak-dose parkinsonian disability (Friedman test, $F_{(3,24)} = 5.081$; n = 7; $P > 0.05$; Fig. 5B). Clozapine also reduced peak-dose levodopa-induced dyskinesia (Friedman test followed by Dunn's multiple-comparison test, $F_{(3,24)} = 9.722$; n = 7; $P < 0.05$; Fig. 5C).

Apomorphine

Apomorphine (0.03 mg/kg s.c.) significantly reversed parkinsonism compared to vehicle (Kruskal–Wallis fol-

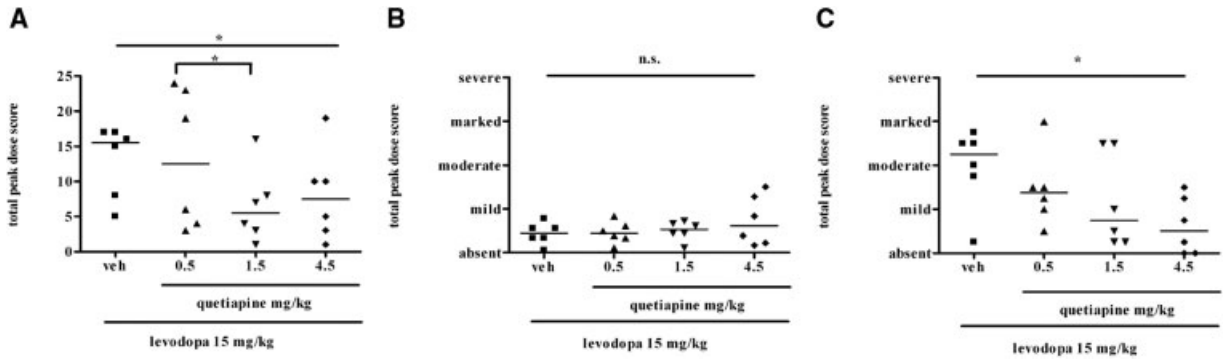

FIG. 4. Effect of quetiapine and levodopa in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Total peak-dose psychosis-like behaviors; **(B)** peak-dose parkinsonian disability; and **(C)** peak-dose dyskinesia as measured using rating scales following administration of vehicle/quetiapine 0.5 1.5, and 4.5 mg/kg p.o. with levodopa methyl ester 15 mg/kg (+ 3.75 mg/kg benserazide) s.c. Data show individual animals; bars represent median total peak-dose scores at 40 to 80 minutes following drug administration. Asterisk, $P < 0.05$, Friedman test followed by Dunn's multiple-comparison test; n = 6.

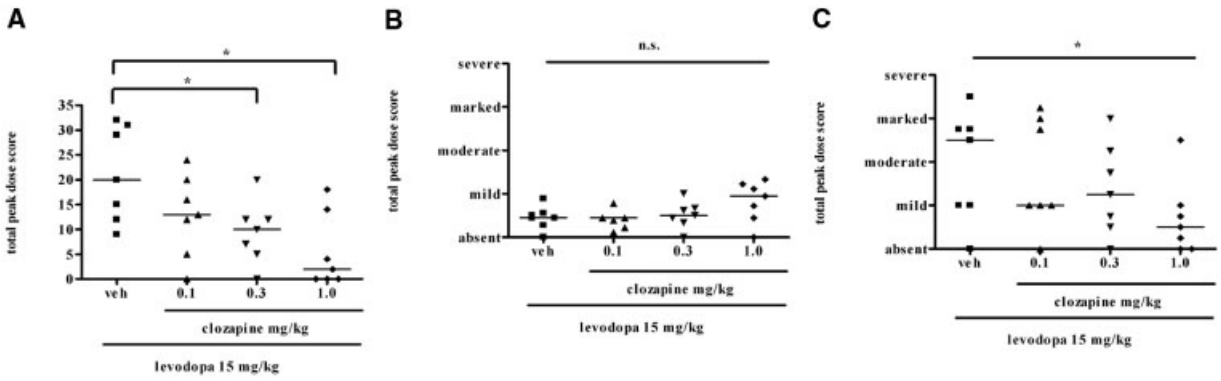

FIG. 5. Effect of clozapine and levodopa in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Total peak-dose psychosis-like behaviors; **(B)** peak-dose parkinsonian disability; and **(C)** peak-dose dyskinesia as measured using rating scales following administration of vehicle/clozapine 0.1, 0.3, and 1.0 mg/kg s.c. with levodopa methyl ester 15 mg/kg (+ 3.75 mg/kg benserazide) s.c. Data show individual animals; bars represent median total peak-dose scores at 40 to 80 minutes following drug administration. $*P < 0.05$, Friedman test followed by Dunn's multiple-comparison test; n = 7.

lowed by Dunn's multiple-comparison test, $F_{(2,18)} = 14.22$; n = 4 to 7; $P < 0.01$; Fig. 6A). There was no significant difference in peak-dose parkinsonian disability between apomorphine 0.03 mg/kg and levodopa methyl ester 15 mg/kg (Kruskal–Wallis followed by Dunn's multiple-comparison test, n = 4 to 7; $P > 0.05$; Fig. 6A). In addition, there was no significant difference in peak-dose dyskinesia scores between apomorphine 0.03 mg/kg and levodopa methyl ester 15 mg/kg (Mann–Whitney test, n = 4 to 7; $P > 0.05$; Fig. 6B). In contrast, apomorphine 0.03 mg/kg induced a significant increase in psychosis-like behavior compared to levodopa methyl ester 15 mg/kg (Mann–Whitney test, n = 4 to 7; $P < 0.05$; Fig. 6C). The apomorphine-induced psychosis-like behavioral response was predominantly due to a significant increase in agitation and hyperkinesia with animals experiencing persistent, fast, explosive movement, as well as an increase in stereotypic behavior consisting of repetitive running around the cage (Mann–Whitney test, n = 4 to 7; $P < 0.05$ for both behaviors).

DISCUSSION

The MPTP-lesioned marmoset model of advanced PD exhibits abnormal psychotomimetic behaviors that are readily distinguishable and pharmacologically distinct from dyskinesia and parkinsonism. These behaviors can be quantified using the presently described psychosis-like behavior rating scale. The study shows that the pharmacological response of these behaviors mimics the pharmacology of psychotic symptoms in a PD patient and thus this model may be used for predictive testing of novel therapeutics for PD patients both in determining the potential to increase psychosis and to treat psychosis in PD patients.

Phenomenology of Psychosis-Like Behaviors

The repertoire of psychotomimetic behaviors exhibited by these animals comprising agitation, hallucinatory-like response, obsessive grooming, and stereotypies is identical to the behaviors we have previously described.[25,31,33] Prior studies in both MPTP-lesioned mar-

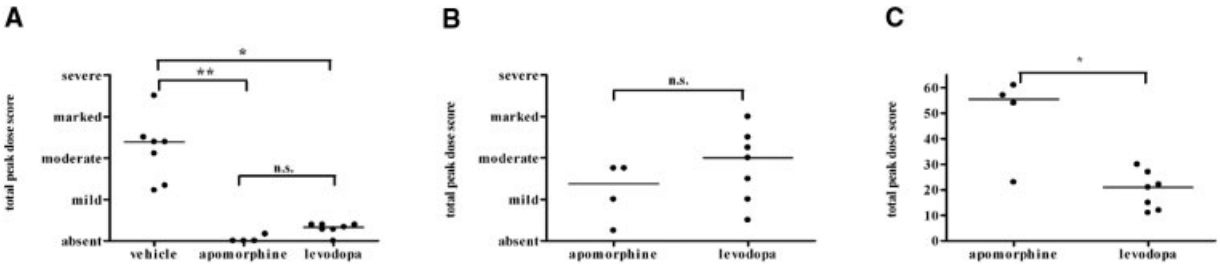

FIG. 6. Effect of apomorphine 0.03 mg/kg and levodopa methyl ester 15 mg/kg in the MPTP-lesioned marmoset model of Parkinson's disease. **(A)** Peak-dose parkinsonian disability; **(B)** peak-dose dyskinesia; and **(C)** peak-dose total psychosis-like behaviors as measured using rating scales. Data show individual animals; bars represent median total peak-dose scores at 10 to 50 minutes for apomorphine 0.03 mg/kg and 40 to 80 minutes following levodopa–methyl ester 15 mg/kg (+ 3.75 mg/kg benserazide) s.c. Panel A: $*P < 0.05$; $**P < 0.01$, Kruskal–Wallis followed by Dunn's multiple-comparison test. Panel C: $*P < 0.05$, compared to levodopa methyl ester, Mann–Whitney test; n = 4 to 7.

mosets and macaques have commented on certain of these behaviors, including agitation,[36] climbing behavior,[37] and hallucinatory-like behavior[38] but without adequate description or quantification. Only one prior study in MPTP-lesioned macaques has attempted to rate hyperactivity, where three components—excitability, irritability, and aggressive behaviors—were rated on a scale of 0 to 2.[34]

The four categories of psychosis-like behaviors we assess may represent classes of activity that regularly occur as part of the spectrum of neuropsychiatric problems experienced by PD patients. Thus, hyperkinesia and driven behavior or vocalization may represent agitation and mania. Often, PD patients report an elevation of mood that occurs with dopaminergic medication. However, in some cases, the so-called dopamine dysregulation syndrome occurs, which in the context of compulsive and excessive dopaminergic medication can result in psychomotor agitation and hyperactivity, increased excitability, hypomania, or mania.[39,40] These patients can also experience a range of symptoms including hypersexuality, pathological gambling and shopping, aggression, and compulsive eating.

The staring and tracking behavior seen in the present study possibly represent attention and orientating responses to nonapparent stimuli and may correlate to hallucinations seen in PD patients. These animals are well acclimatized to the study cages and room and are left undisturbed for the duration of the experiment to minimize any possible external cues. Such activities have also been described in long-term amphetamine-treated macaques, including staring off into space and swatting or grasping at nonexistent objects[27] and thus may represent hallucinations. PD patients often experience hallucinations that range from illusions to well-formed visual hallucinations. In addition, but less frequently, auditory and tactile hallucinations may occur. It is unclear whether the marmoset is capable of experiencing hallucinations of this nature, but clearly the described activity is abnormal and may represent a correlate of that experienced in PD.

The excessive scratching exhibited by these animals may correspond to obsessive–compulsive behavior. In amphetamine-treated macaques, excessive and fixated grooming to the extent of inducing skin lesions (parasitotic grooming) has been described.[27] The marmosets did not exhibit precisely this form of behavior but some animals did exhibit excessive scratching (but nonmutilating), unrelated to s.c. injection sites, as has also been observed during the levodopa-priming process when the animals were treated with oral levodopa.[31]

The motor stereotypies, when present, were animal-specific, i.e., an animal would exhibit one type of behavior repeatedly. The term "stereotypy" used here describes a whole animal activity and not a single limb or body part movement. The motor behaviors exhibited in this group of animals, i.e., side-to-side jumping, fiddling with bars, running in circles, and excessive and repetitive head checking, reflect exaggerations of a marmoset's normal range of activity. These behaviors are clearly distinct from chorea and dystonia and therefore are not part of the phenomenology of dyskinesia in the marmoset. In amphetamine-treated and cocaine-treated primates, similar motor stereotypies are reported and consist of pacing, circling, head swinging, repetitive hand movements, and grasping or fiddling with the bars.[27,41,42] Some PD patients have been reported to exhibit stereotypical behavior termed "punding," which occurs following high doses of dopaminergic agents. Here patients will repeatedly perform the same seemingly purposeless task, often related to a prior trade or hobby.[43,44]

Effect of Levodopa Dose and Apomorphine on Psychosis-Like Behaviors

There was a dose-dependent increase in total peak-dose psychosis-like behaviors following treatment with levodopa. At the same time, no change in either reversal of parkinsonian disability or severity of dyskinesia was observed demonstrating that using the present rating scale, assessment of psychosis-like behavior can be separated from that of both parkinsonism and dyskinesia. A dose of 15 mg/kg levodopa methyl ester was used in all subsequent studies as this dose induced a significant increase in psychosis-like behaviors.

Treatment with the mixed dopamine receptor agonist apomorphine resulted in increased total psychosis-like behaviors, which consisted primarily of agitation, particularly hyperkinesia and stereotypies. Hyperactivity induced by apomorphine (0.03 mg/kg) in the MPTP-lesioned macaque has been previously described.[34] Indeed, due to the marked increase in speed of movement induced by apomorphine in our study, no further studies were performed due to the potential risk of animals to harm themselves. This psychosis-like behavior was clearly separate from dyskinesia, which was not increased following apomorphine treatment as compared to levodopa. Clinical practice has suggested that PD patients who use dopamine agonists such as intermittent s.c. apomorphine or cabergoline are at higher risk of developing neuropsychiatric behaviors and punding.[39,43] In addition, recent retrospective reports have suggested that certain dopamine agonists such as pramipexole may be associated with compulsive behaviors.[45] However, the

exact relationship of psychosis to stimulation of particular subtypes of dopamine receptor or particular classes of dopamine agonists is not known. Further studies are underway to investigate this using the MPTP-lesioned primate.

It is not clear whether all aspects of the syndrome have similar mechanisms but the association between stereotypies and dopamine is well documented. Dopamine agonists and amphetamine or cocaine will induce stereotypies in normal rodents[46–48] and, as described above, in primates. The pathophysiology of stereotypies has been suggested to relate to cortico–basal ganglia circuits involving the lateral and ventral striatum.[48,49] Thus, the development of stereotypies in the long-term levodopa-treated MPTP-lesioned marmoset is probably related to excess dopaminergic neurotransmission; however, the precise neural circuits or subtypes of dopaminergic receptor involved are unknown. As characterization of this model progresses further, it may prove possible to dissect differences in the pharmacology of different components of these abnormal behaviors.

Indeed, hallucinatory-like behavior did not correlate with the dose of levodopa or use of apomorphine. This finding is consistent with the literature as although it is well known that dopaminergic drugs can precipitate hallucinations, studies in PD patients have previously shown that there is no significant difference in the level of hallucinations induced by different doses of levodopa or dopamine agonists in patients.[6,9,50,51]

Effect of Amantadine

Amantadine reduced levodopa-induced dyskinesia without affecting parkinsonian disability; this precisely correlates with clinical practice where amantadine is used as an effective treatment for peak-dose dyskinesia.[52] The most effective antidyskinetic dose of amantadine used here (10 mg/kg) is higher than prior studies in the MPTP-lesioned marmoset (0.3 mg/kg); however, this prior study only found a significant reduction in dyskinesia after 2 hours[32] and the peak effect of levodopa in our studies was within the first hour. In another study, in MPTP macaques, the most effective antidyskinetic dose was found to be 2.5 mg/kg but in this instance was given twice daily for 3 to 6 days before the effect was measured.[38] The dose employed here enabled a reduction in dyskinesia to be observed in the first hour, over the peak-dose of levodopa after a single dose. Clinically, not all patients will respond to amantadine and the average reduction in dyskinesia is 45% to 60%.[52,53] In this study, amantadine reduced levodopa-induced dyskinesia in three out of seven animals by approximately 60%.

Amantadine has been reported to induce psychosis in PD patients,[52,53] a finding mimicked in the present study. Here we report a significant increase in total psychosis-like behavior following administration of the highest dose of amantadine tested (10 mg/kg). This was particularly prominent in one animal that had a marked increase in agitation with hyperkinesia and also hallucinatory-like behavior. A similar finding of hallucinatory-like behavior has been reported with amantadine, combined with high-dose levodopa, in an MPTP-lesioned macaque.[38] The mechanism of action whereby amantadine reduces peak-dose dyskinesia purportedly involves blockade of overactive glutamatergic NMDA transmission in the caudate–putamen.[54] NMDA receptor antagonists, including phencyclidine (PCP) and ketamine, can produce cognitive and behavioral changes in humans similar to the positive symptoms of schizophrenia.[55] Thus, the mechanism of action of amantadine in inducing psychosis-like behaviors in the present study probably relates to an effect on NMDA receptor-mediated transmission.

Effects of Antipsychotic Drugs

The pattern of behaviors induced by the typical neuroleptic, haloperidol, and the atypical neuroleptics, quetiapine and clozapine, in the present study was essentially in keeping with that found in clinical practice, suggesting that this model is generally predictive of the action of typical and atypical neuroleptics in PD patients. Haloperidol reduced psychosis-like behaviors, particularly stereotypies, in a dose-dependent manner, but at the expense of increased parkinsonian disability. Similarly, in patients with PD, haloperidol can reduce psychosis but worsens parkinsonism.[14] Thus, in general, such typical neuroleptics are contraindicated for use in PD patients.

The atypical neuroleptic clozapine also reduced psychosis-like behaviors, particular those in the hallucinatory component of the scale, but without significant exacerbation of parkinsonian disability. In double-blind randomized placebo-controlled studies, clozapine has been demonstrated to reduce psychosis significantly, without exacerbation of parkinsonism.[18,19] Clozapine also significantly reduced dyskinesia without worsening parkinsonism. In a clinical study, clozapine, at similar dose to that used to treat psychosis (mean dose, 39.4 mg/day), also significantly reduced dyskinesia without worsening parkinsonism.[56]

Quetiapine also reduced psychosis-like behaviors in the MPTP-lesioned marmoset without affecting parkinsonism and has been shown to reduce psychosis in PD in two open-label studies.[57,58] A recent double-blind placebo-controlled trial, however, failed to show any signifi-

cant benefit of quetiapine on psychosis but did find quetiapine had no detrimental effects on parkinsonism.[21] This variability in response to quetiapine was noted in this study where, at the lowest dose of quetiapine, 0.5 mg/kg, although overall there was a significant decrease in median psychosis-like activity, three animals displayed an increase in psychosis-like behavior. The cause of this variability is unknown. Quetiapine also reduced levodopa-induced dyskinesia. In clinical trials, however, quetiapine at both low (25 mg/day) and high doses (75–200 mg/day) failed to reduce dyskinesia significantly.[21,59] This difference may reflect the higher dose of quetiapine used in the MPTP-marmoset, 4.5 mg/kg, as opposed to 2.8 mg/kg (equivalent dose in PD patient using 200 mg).

Haloperidol is thought to reduce psychosis via blockade of mesolimbic dopamine D_2 receptors.[60,61] However, blockade of nigrostriatal dopamine D_2 receptors worsens parkinsonian symptoms.[62] Haloperidol specifically reduced stereotypies in the MPTP-lesioned marmoset without significant effect on other psychosis-like behaviors. Thus, as previously suggested, it is possible that stereotypies are mediated by a dopaminergic mechanism. Furthermore, these findings suggest that psychosis-like behaviors unaffected by haloperidol may be mediated via other nondopaminergic receptor mechanisms. For example, 5-HT receptors may be involved.[63,64] The atypical neuroleptics display activity at a wide range of receptors; thus, it has been suggested that the mechanism underlying the ability of atypical neuroleptics to reduce psychosis without affecting parkinsonism may relate to relative D_2 versus 5-$HT_{2A/C}$ receptor selectivity.[65] The ability of clozapine to reduce hallucinatory-like behavior preferentially in the MPTP-lesioned primate may reflect this receptor selectivity.

A potential side effect of neuroleptics is somnolence.[66] However, no drowsiness was noted in these animals at any time point. In addition, there was no significant effect on parkinsonism with these agents except at the highest dose of haloperidol; thus, the effects on reducing psychosis-like behaviors are unlikely to be due to a simple nonspecific reduction in motor function. In addition, neuroleptics such as clozapine have also been associated with anxiolytic properties in PD.[67] The effect on anxiety per se was not formally tested in this study. However, we note that, overall, the profile of effects of neuroleptics on psychosis-like behavior observed here was similar to effects on psychosis in PD. Thus, if anxiolytic actions were responsible for reductions in psychosis-like behaviors, as rated here, they might have potential benefit in PD patients with psychotic symptoms. However, this notwithstanding, we propose that it is unlikely that the reduction in levodopa-induced behavioral responses by the neuroleptics could be ascribed to reduction in anxiety per se as, in general, PD patients report anxiety as an *off* period problem and in fact dopaminergic agents usually alleviate the symptoms.[68]

Shortcomings of Model

The subjective nature of psychotic behaviors can clearly not be assessed in the MPTP-lesioned marmoset; rather, these psychosis-like behaviors might be a physical manifestation of similar processes in the nonhuman primate brain. Thus, the abnormal movements of the head in response to apparent nonstimuli are suggestive of hallucinatory behaviors. The modulation of such behaviors by the pharmacological manipulations applied in the present study in a manner equivalent to that seen with psychosis in the clinic provides evidence that these observed behaviors do indeed correlate with those of the human condition. There are differences in the pathology of parkinsonism induced by MPTP and idiopathic PD, which may result in differences in the presently described psychosis-like behaviors compared to psychosis in PD. Thus, there is a uniform loss of dopamine in the caudate–putamen following MPTP lesioning, unlike the asymmetric loss seen in PD.[69,70] Furthermore, MPTP induces dopamine loss in sensorimotor and associative regions of the striatum with less involvement of limbic circuits.[71,72] An MPTP lesion is often thought of as a dopaminergic lesion; however, in the MPTP-lesioned primate, changes also occur in the serotonergic and noradrenergic systems with cell loss in the dorsal raphe nucleus and locus coeruleus, respectively.[73,74] Thus, nondopaminergic systems that may be involved in psychosis can be effectively modeled in the MPTP primate. Indeed, the data presented here argue for the involvement of both dopaminergic and nondopaminergic mechanisms in the expression of psychotomimetic behaviors.

Future Directions

A useful animal model of a human disease must exhibit reliability and validity. The MPTP-lesioned marmoset model of psychosis-like behaviors demonstrates reliability as the behavior is consistent and stable over time. The present study sought to validate the proposed model of psychosis-like behaviors in the long-term levodopa-treated MPTP marmoset by pharmacological means. The model has face validity as the phenomenology mimics the physical expression of neuropsychiatric problems encountered in PD. There is possible etiological validity as the MPTP-lesioned marmoset after long-term levodopa is unequivocally the best model for advanced PD, when psychosis is most likely to occur.

Future studies are underway to examine possible molecular and biochemical correlates of these behaviors. The particular strength of this model is that it has predictive validity in terms of response to treatments that both exacerbate or attenuate psychosis-like behaviors. The MPTP-lesioned primate may thus represent a useful model for investigating the neural mechanisms underlying psychosis in PD and for developing novel therapeutic strategies prior to clinical studies.

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LEGENDS TO THE VIDEO

Segment 1. Normal: an untreated marmoset showing normal level of motor activity and alertness.

Segment 2. Parkinsonian untreated: following MPTP treatment, this animal demonstrates reduced motor activity, akinesia, hunched posture, and reduced blink rate. The animal is less reactive to stimuli and does not respond to close up filming.

Segment 3. MPTP-lesioned marmoset following long-term levodopa therapy with levodopa-induced dyskinesia: involuntary movements of all limbs, mixture of chorea and dystonia.

MPTP-Lesioned Marmosets Following Long-Term Levodopa Therapy:

Segment 4. Hyperkinesia: fast ballistic movements.

Segment 5. Tracking: following nonapparent stimuli.

Segment 6. Staring: this animal was eating and then stopped and was staring at a nonapparent stimulus for several seconds before resuming eating activity.

Segment 7. Side-to-side jumping: this animal exhibits repetitive purposeless stereotypies (see Segment 8).

Segment 8. Running in circles.

Segment 9. Fiddling with bars: this animal repetitively grasps and scrabbles at corner of cage bars. Also exhibits lower limb dyskinesia.

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